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Editorial

WE are becoming an aging race. The National Office of vital statistics in the U.S. reports a 3% drop from last year in the death rate. This is only one more statistical confirmation of the fact which we have long realized.

In itself this fact would be very encouraging. We can look forward to living longer lives—with time to do the things we want to do. We can die happily—not as Cecil Rhodes did at the age of 50, saying, "So little done, so much to do."

Theoretically, if we returned to the system of taking the advice of our "elders" we should benefit from wiser statesmanship, better statesmanship, and the mature judgment of men who have seen the folly of squabbles and wars.

Unfortunately, with our present knowledge of the physiology of old age, we realize that elderly people are not always clear-minded knowing sages who drop pearls of wisdom every time they open their mouths. They are often confused in their thinking and prone to spend hours in disconnected reminiscing.

After having survived the infectious diseases of childhood and middle age, they are susceptible to the degenerative illnesses of old age. Their arteries become hardened, their brain becomes ischemic, and they—

> "End this strange eventful history,
> In second childishness and mere oblivion,
> Sans teeth, sans eyes, sans taste, sans everything."

This is the tragedy which should be remedied—the unhappy ending to a fruitful life. Since medical science is responsible for our greater expectation of life it is logical that it should do what it can to better the lives of those who have reached a "ripe old age".

A start has been made in this direction. Within the past year a new journal has appeared—"The Journal of Gerontolgy". As stated on the cover the purpose of this journal is "To add life to years, not just years to life."

Some representative titles from this interesting publication are: "Estrogens and Senile Skin"; "Splenectomy for Patients Past Sixty"; "Chronic Pulmonary Disease of Old Rats"; and "Comparative Chronologic Age".

These pioneer ventures into the study of aging should greatly interest us. After all, we are the generation which may see the day when 100 years is not considered an unusual length of time to spend on this pleasant earth.

SYDNEY ROSEN, '48.

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The Etiology of Arteriosclerosis

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ARTERIOSCLEROSIS is defined as non-inflammatory arterial degeneration and includes a variety of pathological types:

1. *Atherosclerosis:* This is a nodular or patchy degeneration of the wall of large and small but not medium sized arteries. The disease is characterized by the development in the subintimal layers, of longitudinal yellow streaks containing lipoid material. The consequent intimal thickening may progress to ulceration of these lipoid plaques, the formation of thrombi on them, or to calcification of the plaques. There is always some degree of associated medial degeneration.

2. *Monkenberg's Sclerosis:* The picture is one of a patchy or encircling degeneration of the media of medium sized arteries. The process, which is the result of medial necrosis, progresses to lime-salt infiltration and even true bone formation.

3. *Diffuse Arteriolar (Hyperplastic) Sclerosis:* This is a disease of arteries of 100 micrans or less, affecting especially the arteries of spleen, pancreas, kidney and adrenal.

In the benign form there are two characteristic features: the first is hyalinization starting in the subendothelium and later involving the whole wall; the second is a splitting of the internal elastic lamina into several layers. This elastic hyperplasia may later replace all muscle fibres of the media.

In the malignant type, there are three features: first, an intimal and medial cellular hyperplasia which gives, on section, the appearance of concentric rings—the so-called "onion skin"; secondly, collagenous and fatty degeneration of the hyperplastic cells; and thirdly, an arteriolar necrosis by which the vessel wall becomes indistinct and often haemorrhagic.

4. *Other diseases,* such as Ideopathic Cystic Medial necrosis which is a frequent forerunner of spontaneous rupture of the aorta or of dissecting aneurysm, are much less common than the other three.

In this paper, the discussion will be limited largely to an investiga-

tion of the etiology of atherosclerosis and will include the other types only for comparison.

What are the possible mechanisms by which arterial degeneration may be produced? They are the following:

1. Essential cellular death as a part of the ageing process.
2. Anoxia of the vessel wall.
3. Excessive contraction of the muscular elements of the wall or excessive relaxation.
4. Excessively high or low pressures in the arterial lumen.
5. Metabolic disturbances of the cells of the vessel wall other than on an anoxic basis, i.e., disturbances of the fat, protein or carbohydrate utilization within the vessel.

Each of these will now be reviewed in detail.

1. Essential cellular death as a part of the ageing process. At first glance this theory appears to be a logical one. Arteriosclerosis is often looked upon as a problem for the geriatrician, looked forward to as one of those inevitable concomitants of advancing years.

Everyone agrees that loss of elasticity in the arteries, like the crow's foot in the eye, begins soon after maturity and progresses irreversibly as the senile state approaches. However, loss of arterial elasticity, reflected clinically by a systolic hypertension without diastolic hypertension, is often mistakenly termed arteriosclerosis when no such disease exists. Many elderly persons have this picture of inelastia without arteriosclerosis, and, on the other hand, many young persons exhibit arteriosclerosis without inelastia.

To regard arteriosclerosis as a disease of the ageing process, without first excluding all other possible etiological factors, is to by-pass a vast field of scientific investigation and to despair of any eventual prevention or treatment.

2. Anoxia of the vessel wall: This subject involves a study of the various possible methods by which anoxia may occur. These are:

(a) Interference with the circulation of the vasa vasorum.
(b) Interference with the diffusion of oxygen through the endothelium.
(c) Interference with the proper oxygenation of blood in the whole organism.

If anoxia is to produce arterial degenerative lesions, it must do so by virtue of a primary necrosis and be followed by lipoid deposition secondarily.

The possibility that thrombosis and haemorrhage in the vasa vasorum may account for such arterial degeneration was thoroughly investigated by Winternitz, Thomas and LeCompte in 1938. By careful

injection technique they were able to show that the vascularity of the arterial wall, which they found to be minimal in young healthy adults, was greatly increased by arterial disease and in old age aside from the presence of arterial disease. Winternitz and his co-workers believed that this increased vascularity predisposed to vascular accidents in the vasa vasorum.

They noticed that haemorrhages, especially, occurred quite frequently in the subintimal layers of the arterial wall and that they occurred commonly in those sites where atherosclerosis is most prone to develop—the arch and lower portion of the descending aorta. They believed, because of inflammatory stimulation, that each haemorrhage led to a proliferation of more vessels and this in turn predisposed to other haemorrhages. They thought that, following such haemorrhagic necrosis, the breakdown products of dead cells were crystalized locally in the form of lipoids in much the same way that haemorrhage into adenomata of the thyroid leads to a production of cholesterol deposits in this gland.

The second possible mechanism of the production of anoxia in the vessel wall, that of interference with the diffusion of oxygen through the endothelium, was investigated by W. C. Hueper. After mixing solutions of such inert macromolecular substances as polyvinyl alcohol, pectin, methyl cellulose or gum arabic with specimens of blood, he noticed that the oxygenation speed of the red blood cells was greatly prolonged. This he belived due to the formation of a layer of the relatively impermeable macromolecular substance over the cell membrane, preventing proper oxygen exchange into the red cell.

Having established this fact, he proceeded to inject solutions of these substances into the circulating blood of rabbits, dogs and rats, on the theory that, if these substances interfered with oxygenation of the red cells by a film formation, they would affect the vascular lining similarly. In due time he was able to demonstrate the development of foam cells, instead of being filled with lipoid, contained the substance atheromata similar in appearance to those of athersclerosis but the injected. This change was most noticeable in the aorta and other large vessels. The endothelium was converted into large pale foam cells which projected into the subendothelial layer and formed extensions between the fibres of the media. The vasa vasorum were similarly affected. After a period of time, he observed a fibrotic reaction in the subendothelium and media which in some animals progressed to calcification. Ulceration in the areas of intimal thickening was sometimes seen.

Hueper believed that the anoxic process produced by the non-permeable film stimulated a natural defensive reaction — a conversion of the endothelial cells into phagocytes which were able to engulf the offending membrane.

In comparing this artificial atherosclerosis with the human disease, Hueper pointed out that cholesterol may be similarly deposited on the endothelium and lead to the same result through such an anoxic process. He found that when cholesterol was added to a specimen of blood, the same prolongation of oxygenation speed of red cells occurred as in his previous experiment with artificial substances. He therefore postulated that atherosclerosis may occur in man as a result of two factors. First, an increased blood cholesterol level as in hypothyroidism, diabetes mellitus, essential xanthomatosis, lipoid nephrosis and excessive dietary intake of cholesterol. He believed that this latter condition accounted for an increased incidence and severity of atherosclerosis among certain Asiatic tribes who live on fermented mare's milk and meat. The second factor, he believed to be a reduction in stability of the colloidal state of cholesterol in blood plasma. A vibration effect produced by eddying of blood seemed to be chiefly responsible. This phenomenon was comparable to the production of flocculation elicited by shaking in the Kahn test. The sites of predilection of atherosclerosis in the aorta offer substantiation for this theory as the greatest whirl formation probably corresponds to the bifurcation and arch of the aorta. Rapid fluctuations in blood flow in the aorta due to systolic thrust and diastolic recoil of the semilunar valves were also thought to produce sufficient vibration to precipitate cholesterol from its colloidal state. The third possible mechanism for the production of anoxia—a general lowering of the oxygen tension of the blood—was investigated by Campbell in 1935. Although he and other workers succeeded in producing arteriosclerotic changes in experimental animals by a general deprivation of oxygen, other factors enter the etiological picture, especially the associated vasospastic condition, so that it is generally believed that this can have little influence on the production of arteriosclerotic lesions—at least in man.

We now come to a discussion of the third possible mechanism which may be instrumental in the production of arterial degeneration, namely, a decrease or increase in the tonus of the muscular elements of the wall, that is, the effects of hypotonia and hypertonia. Degenerative changes due to hypotonia were produced by Hall, Ettinger and Banting in 1936 following the injection of acetyl choline into rabbits and by Hueper after repeated injections of histamine into dogs. These changes, which were most pronounced in the aorta, myocardial vessels, pulmonary and cerebral arteries, consisted of:

1. hyalinization of the intima
2. condensation of albuminoid material beneath the endothelium
3. hyalinization, fibrosis and cyst formation in the media
4. calcification of the elastic laminae of the aorta and cerebral arteries.

A similar pathological picture has been seen in man accompanying

fatal cases of acute infectious fevers such as diphtheria, tetanus or typhoid and following exposure to such chemicals as volatile nitrites, carbon monoxide, arsenic or benzol.

To estimate the effect of excessive contraction of the muscle wall, Hueper experimented with the injection of various vaso-constrictor agents—nicotine and adrenalin and the digitalis glucosides. Paunz administered tyramine and tyrosine, precursor substances of adrenalin. After repeated injections they noticed that the small arteries of experimental animals developed a primary hyaline and fibrous intimal thickening and a secondary medial fibrosis and calcification. The large and medium sized arteries were not affected.

In assessing the role of changes in intra-arterial pressure, previously mentioned as the fourth possible mechanism of arterial degeneration, we will state frankly that hypotension has been found to have no effect other than in the production of endarteritis obliterans. This may be produced in arteries on the arterial side of an arterio-venous anastomosis, in the uterine and ovarian arteries after the menopause, in the umbilical arteries and ductus arteriosus after birth or in arteries in scar tissue which have a low functional demand.

Hypertension, on the other hand, has been shown by Goldblatt and others to be responsible for the changes of diffuse hyperlastic sclerosis and in the pulmonary artery may be responsible for intimal thickening and medial fibrosis and calcification seen in cases of congenital patent ductus arteriosis, septal defects, mitral stenosis and emphysema.

However, no evidence is at hand to show that it has a direct etiological role in the production of atherosclerosis.

In reviewing the position of changes in vascular tonus and changes in intravascular pressure in the etiology of atherosclerosis, it is obvious that neither of these may, *per se*, be responsible for all changes of atherosclerosis. However, it is also obvious that they may produce rather non-specific changes in arteries affected by atherosclerosis. Therefore, it remains to be seen whether or not these changes may have precursor or localizing effects upon the eventual development of atheromata.

It remains to discuss the last and most complex mechanism through which arterial degeneration may possibly be produced—that of disturbances of arterial cell metabolism other than of the anoxic type already reviewed. It has been found that disturbed protein and carbohydrate metabolism have little, if anything, to do with the development of arterial disease. The discussion revolves, then, chiefly around lipoidal metabolism, especially cholesterol metabolism.

A glance at the various existing theories of the role of cholesterol in atherosclerosis may best serve to introduce this subject.

Virchow's original conception of the formation of atheromata, later revived by Aschoff, was termed the "Imbibition Theory" and expressed the belief that cholesterol was absorbed or filtered through the endothelium in areas where previous mechanical strain had produced some loosening of the connective tissue ground substance. They believed, however, that before such "intimal imbition" might occur, an increased blood cholesterol level had to be present.

Leary, in 1934, expounded another theory of the origin of cholesterol deposits in atherosclerosis which differed from that of Virchow and Aschoff in that it implied an active transport of cholesterol by means of phagocytes into the subendothelial layers of the vessels. On feeding rabbits a high cholesterol diet he noticed that lipoid accumulated in the parenchymatous cells of the liver, but, on further cholesterol feeding, was transferred to the Kupfer cells and reticuloendothelial cells of other organs. Thus, Leary believed that some of these phagocytic cells were freed into the venous sinuses, passed to the heart, then through the lung capillaries and were finally deposited by that rather nebulous force of "positive chemotaxis" on the endothelium of the aorta where they made their way into its subendothelial layers. Here the cholesterol was freed from the reticuloendothelial cells, now called foam cells, and, by acting as a tissue irritant, tended to produce an overgrowth of connective tissue. That is, the deposited lipoid was the initial step, the sclerosis secondary to it.

The work of Bloor in 1943 turned yet another beacon on this searching problem. It was known, from the studies of Shope and Sperry that the transport of fatty acid from the intestine to the cells where it is utilized occurred in the form of a combined molecule of fatty acid and cholesterol—that is, by an esterified cholesterol molecule. In the tissues, this ester is broken down into fatty acids and cholesterol by an enzyme, esterase, which circulates in the blood. The fatty acid is utilized by the cell and the cholesterol diffuses into the circulation from which it is later removed. Thus, according to Bloor, two mechanisms for the deposition of cholesterol in the tissues are possible: first, that if cholesterol esters are present in such great concentration that the enzymic system is unable to cope with their breakdown, the excess lipoid will accumulate in the tissues; secondly, that if the enzymic system itself becomes defective, lipoid accumulation may similarly occur.

These are the most popular theories of the day but the acceptance of any one of them must necessarily be determined by a better understanding of the role of cholesterol in body function. In this regard, several questions come to mind, some of which may be at least partially answerable.

1. May hyperlipemia produce atherosclerosis?
2. What are the effects on the blood lipoid level of changes in the amount of lipoid ingested?
3. What is the relationship of age to blood lipoid level?
4. What factors have a positive or negative effect on blood lipoid level?
5. May atherosclerosis develop without hyperlipemia?
6. Does hyperlipemia necessarily produce atherosclerosis?

1. *May hyperlipemia produce atherosclerosis?* The answer is "yes"—if hyperlipemia can be produced experimentally, atherosclerotic lesions may develop. Anitschkow first demonstrated this in 1913 by feeding large amounts of cholesterol to rabbits. He noticed a marked blood cholesterol level increase associated with the development of typical atherosclerotic lesions in the blood vessels. Many workers since his time have produced the same results.

2. *What are the effects on the blood lipoid level of changes in the amount of cholesterol ingested?* After Anitschkow's initial discovery it was found that to produce a significant elevation of the blood cholesterol level in omnivorous animals, such as the dog or cat, required disproportionally large amounts of cholesterol in the feedings.

It has also been demonstrated in man that after a fatty meal the blood shows an elevation of neutral fat and phosphatide but only a very slight and transient elevation of cholesterol. After a careful study of nine patients, Turner and Steiner found no relation between the type of diet—either high or low cholesterol—and the level of the blood cholesterol.

The difference between the ability of herbivora and omnivora to handle cholesterol was investigated by Irving H. Page who came to the conclusion that their ability to metabolize cholesterol was the same but the ability of herbivora to excrete sterols was greatly limited. The excretion of cholesterol is mainly by two routes—first, a very small amount as cholesterol itself into the urine and faeces, and secondly, most of it as coprosterol excreted into the faeces. It has been found that in omnivorous animals there is an increase in the urinary and fecal sterols after the administration of cholesterol. It has been noted also that the administration of cholesterol to omnivorous animals produces a fatty degeneration of the liver (cholesterol plus fatty acid) but this is more difficult to produce in herbivorous animals. Herbivorous animals tend to build up their blood level, while omnivorous animals either excrete or store an excess of ingested lipoid. Thus it is possible to explain the failure of elevation of blood cholesterol in man following the ingestion of fatty meals.

3. *What is the relationship of age to blood cholesterol level?* In 1935, Page, Kirk and others carried out plasma lipoid estimations

on a group of healthy men between the ages of 29 and 90 years. These subjects were on restricted diets. They found in this series not the slightest evidence to indicate that age has any bearing either on composition or amount of plasma lipoids.

Old age, then, apparently produces no hyperlipemia.

4. *What conditions do have a positive or negative effect on blood lipoid level?* Thyriod and potassium iodide were shown by Turner in 1933 when administered to rabbits on a high cholesterol diet to prevent the development of atheromata. The mechanism of their action seemed to be by prevention of hypercholesterolemia.

Testosterone and oestradiol were found also to inhibit hypercholesterolemia and prevent atheromatous depositions in the aorta of female rabbits on cholesterol diets.

The addition of lecithin to a cholesterol diet has been found to cause more rapid and pronounced hyperlipemia. In fact, a diet of 100 gm. of powdered egg-yolk daily (lecithin 14 gm., cholesterol 8 gm.) produced in ten of Steiner's patients an increase in blood cholesterol of from 40 to 218 mgs. per 100 cc.

An alcohol-cholesterol diet may increase the blood cholesterol level much more than a diet of cholesterol alone but the amount of atherosclerosis developing is much less.

5. *May atherosclerosis develop without hyperlipemia?* The answer to this is suggested by the answer to a previous question and further evidence is offered by Landé and Sperry who were unable to find any relation between cholesterol content of serum and degree of atherosclerosis on post-mortem examination of supposedly healthy persons dying suddenly by violence.

These results were later substantiated clinically by Kountz and others working with a group of cases of coronary artery sclerosis diagnosed by electrocardiogram. They found no significant elevation of blood cholesterol level.

6. *Does hyperlipemia necessarily produce atherosclerosis?* Although iodides had been shown to prevent atherosclerosis in rabbits by the prevention of hyperlipemia as already mentioned, it remained for Page and Bernhard, in 1935, to demonstrate that atherosclerosis may be prevented in spite of an elevated cholesterol level.

They found that if di-iodide of ricinsterolic acid was administered to rabbits with an experimentally induced hyperlipemia, the hyperlipemia was not reduced but no atheromata developed. They concluded that the action of this substance was concerned not with the adsorption,

utilization or excretion of cholesterol but rather with the mechanism of reception of the arterial wall to cholesterol deposition.

With these questions answered, we are now able to review the various theories of the role of cholesterol with a more critical eye.

From the foregoing observations it is evident that we must divide atherosclerosis into two varieties on the basis of etiology at least—one with hypercholesterolemia, the other without.

In the hyperlipemic type, cholesterol may simply be imbibed in a chemical fashion into the subendothelium as Virchow and Aschoff believed, or it may be carried there by phagocytic cells as described by Leary. On the other hand, it may be the result of a failure of dissociation of the ester of fatty acid and cholesterol with the accumulation of this lipoid locally.

In the latter case, cholesterol would be present in the lesions, only in the esterified form with very little, or no, free cholesterol since if the esterase system cannot break down the excess ester, only the ester and no free cholesterol is deposited. Page and his co-workers carried out chemical analyses of human atherosclerotic aortas and found that the plaques contained free cholesterol 18% of the total lipoids, and esterified cholesterol 39%. We conclude from these results that the production of atheromata cannot be purely on the basis of an overloaded esterase system. Page compared these figures with the relative proportions of the plasma lipoids and found remarkably similar ratios: free cholesterol 12% of total lipoids; ester 36% of total lipoids. Thus, Page has demonstrated that lipoids in atheromata must be derived from the blood by a process which does not alter the relative proportions of each lipoid. He has also demonstrated that, in experimental atherosclerosis, qualitative and quantitative estimations of serum lipoid reveal normal proportions of the normal lipoids even though only cholesterol be increased in the diet. In such animals, analysis of the atheromatous plaques parallels the blood lipoid picture, that is, it demonstrates a lipoid distribution with ratios identical with normal serum values. Thus, besides cholesterol, other lipoids are involved in the formation of experimental atheromata just as in the spontaneous human disease.

Coming back to the theory of Virchow-Aschoff and that of Leary, we find one obstacle in the way of accepting either of them as a basis for atherosclerosis with hyperlipemia. The obstacle lies in the experiment by Page, in which di-iodide of ricinsterolic acid prevented the development of atheromata in spite of hypercholesterolemia. Alcohol was found to have a similar effect. Was this phenomenon due to an inhibition by the drug of the imbibing power of the endothelium or of the phagocytic power of the foam cells or, on the other hand, was it

due to some effect on a third, entirely unknown system which plays a part in the deposition of cholesterol? In any case, it is difficult to reconcile this absence of atheromata in the presence of hyperlipemia with the rather rigid theories of Aschoff or of Leary.

In discussing atherosclerosis without hyperlipemia, we must overlook both these theories. They both imply that hyperlipemia is a necessary fore-runner of atherosclerosis. One might say that hyperlipemia may have been present at some stage in the development of atherosclerosis and so include them on that basis but so far no evidence of this has been offered.

The mechanism of disturbed esterase function with accumulation of cholesterol esters is as much subject to criticism in this type of atherosclerosis as in the first. The plaques present in atherosclerosis unassociated with hyperlipemia are not composed entirely of esters but, again, contain the lipoid elements in the same proportions as found in the serum.

It is obvious, then, that in cases of atherosclerosis without hyperlipemia, we cannot, with our present knowledge, account for their development purely on the basis of disturbed cholesterol metabolism. If any hope of explaining the etiology of atherosclerosis with hyperlipemia exists, it is soon dispelled by a realization of the identical pathological appearance of both these types pointing to one fundamental causative mechanism.

SUMMARY AND CONCLUSIONS

There appear to be two basic concepts of the etiology of atherosclerosis:

1. that damage of some form is inflicted upon the vessel wall, leading to a fibrotic reaction and that, following this, there occurs a deposition of lipoid.
2. that lipoid is initially deposited in the vessel wall and that sclerosis or fibrosis follows as a tissue reaction to foreign substance.

The possible damaging forces may be:

1. anoxia—either from haemorrhages in the vasa vasorum or from the deposition of an impermeable film on the endothelium.
2. physical strains—either as a result of hyper- or hypo-tonus of the vessel wall or of hyper- or hypo-tension inside the vessel.

Attractive as this first concept may be, it fails to explain the intimate relation which this disease may have, in some cases, with diseases upsetting cholesterol metabolism. The theory of haemorrhages in the vasa vasorum fails to explain the occurrence of atheromata in the small arteries.

It seems unlikely, then, that fibrosis or the formation of scar tissue might, in itself, lead to the production of atheromata.

The second basic concept, that lipoid is initially deposited, has already been discussed in an evaluation of the role of disturbed lipoid metabolism. The conclusion was reached that we are unable to account for the development of atheromata purely on the basis of a disturbance in the artery of the utilization of cholesterol.

Thus we come to appreciate the complexity of the etiological mechanisms in arteriosclerosis and we are forced to realize that no solitary factor but rather an interplay of various processes is responsible for this degenerative condition.

Our present inadequate knowledge at least serves to indicate further channels for investigation. One of the most prominent of these is the elucidation of the precise biochemical response of the endothelial cell to cholesterol.

This problem of the etiology of arteriosclerosis is deserving of aggressive and optimistic study. In its solution lies the rescue of man from that tireless enemy who would make of his life, as of his arteries, a frail and unstable shell.

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Curare

By PAUL KEPKAY, '47, AND JOHN R. BARBER, '47

CURARE, once the drug of pure physiology has now beyond any doubt made its debut into the clinical aspect of medicine; and is ever proving to be more useful and valuable. Its history is shrouded in romance and mystery—being used in the upper reaches of Amazonia from earliest times as a potent arrow posion—the "flying death"; and since that time has found its way into detective novels, physiology laboratories, and, more recently, into the realm of practical therapeutics.

In this short paper we will attempt to cover the following aspects of curare;

1. History.
2. Pharmacology and toxicology.
3. Clinical applications.

1. *History:* can be studied under three phases;
   (a) Ancient.
   (b) Pre-therapeutic.
   (c) Therapeutic.

(a) *Ancient*

There are references in the ancient classics to arrow poisons which some consider to be curare. Notable among these writings are:

1. Homer and his Odyssey.
2. Virgil's Aenid.
3. The darts of Appolo which carried a "pestilence".
4. Biblical (Job 6:4)—"For the arrows of the Almighty are within me, the poison whereof drinketh up my spirit".
5. The ancient association of bows and arrows with poisons; toxicology being derived from the Greek "toxon" meaning bow.

However, the earliest actual reference to its use is in Hakluyt's description of Sir Walter Raleigh's voyage up the Orinocco in 1595 when even then the Indians were using it as an arrow poison. With regard to this poison Sir Walter Raleigh himself writes the following: "There was nothing whereof I was more curious than to find the true remedies of these poysoned arrows; for besides the mortalitie of the wound they make, the partie shotte endureth the most insufferable torment in the world, and abideth a most ugly and lamentable death, sometimes dying starke mad, sometimes their bowels breaking out of their bellies; which are presently discoloured as blacke as pitch, and so unsavoury, as no man can endure to cure, or to attend them. And it

is more strange to know, that in all this time, there was never a Spaniard either by gift or torment that could attain the true knowledge of the cure, although they have martyred and put to invented torture I know not how many of them. But every one of these Indians know it not, no, not one among thousands, but their soothsayers and priests who do conceal it, and only teach it but from father to the sonne".

(b) *Pre-Therapeutic*

In 1814 Watterton and Brodie observed that asphyxia from respiratory paralysis was the cause of death in curare poisoning. This was confirmed in 1840 by Claude Bernard in a series of physiological experiments (which will be considered later).

Alexander von Humbolt (1821) was the first to witness the making of curare; and it was he who made it clear that there were several different arrow poisons in use by the South American Indians. His contemporary, Sir Robert Schonburgk (1857), classed the plants from which curare is made in the genus Strychnos. (Note: that some of these Strychnos curares contain in addition to the peripheral paralyzing curare, a central convulsant action component due to strychnine.) Soon the active principles were isolated from the crude curare;

(a) The "Syrupy Body" of Boussingault & Roulin (1828).

(b) A crystalline form by Preyer (1865).

(c) Another crystalline alkaloid "Curine" by Boehm (1896); who also got a 5% yield of curine direct from the bark of the Strychnos toxifera.

We must also note "The Geographic Distribution" of the curare types; all of them being found in the Strychnos species in Tropical America; (a) Upper Amazonia, (b) Upper reaches of the Orinocco, (c) Kanaku Mountains of Br. Guiana. Using such a geographical basis Boehm (1895) classified the "curares" with regard to the types of containers in which they were dispatched from the forest regions of production;

(1) A small earthenware pot.

(2) A hollowed gourd or "calabash".

(3) The interior of a bamboo cane.

He described three alkaloids as being present in "pot" curare, an additional alkaloid in the "calabash" curare, and two additional different ones in the "bamboo" or "tube" curare. However, the vehicular classification failed to distinguish geographical types accurately. In consequence, we now classify curare according to West's Schema:

1. Paralysis is the sine qua non of curare.
2. A convulsant property, like that of strychnine, is found in some specimens.

3. These specimens also exert a specific respiratory effect in which breathing becomes slowed, laboured, and deliberate; progressing to respiratory failure before obvious skeletal weakness and generalized paralysis occur.
4. All specimens produce the "lissive action" of West or selective removal of pathologic rigidities without apparent diminution in voluntary power (as in pyramidal tract lesion).

(c) *Therapeutic*

The therapeutic phase dates from 1938 when Richard G. Gill, an American, led an expedition into the wilderness of the Amazonian jungle to obtain curare and a knowledge of its manufacture in order that it could be used as a scientific medicine in the treatment of spastic disease. He himself had just recovered from spastic paralysis. In his book "White Water And Black Magic", he describes the difficulties and dangers in his quest for the "flying death" and his final success. Sponsored by E. R. Squibb & Sons, Prof. A. R. McIntyre of the University of Nebraska made the first thorough pharmacological study of curare. It was offered to the medical profession for study under the name of "Intocostrin". This is standardized by biological assay to contain the equivalent of .02 gms. per c.c. of a standard drug.

Other notable names in this therapeutic phase are Rennett, Cullen & Quinn, Burman, and Griffith and Johnson.

2. *Pharmacology*

The pharmacological aspects will be considered under:

(a) Availability
(b) Preparations
(c) Actions
(d) Toxicology

(a) Availability:

As yet no method of synthesizing curare has been discovered and our only sources are in the South American jungle. Curare is a gummy substance obtained by brewing the stems, leaves, and roots of the Strychnos Toxifera. Let it be noted that this classification in the strychnos family is erroneous—as the action of course is the direct antithesis to that of strychnine. In fact curare has been used as an antidote in cases of strychnine poisoning. The best criterion for the crude drug—either by standards of the Indian hunter or by those of the physiologists—is that of a potent poison whose predominant action is paralysis of voluntary muscles. Although curare was tried by many about the middle of the last century, for many and varied convulsive states, its varying toxicity made it such an unreliable therapeutic tool that it was soon abandoned by clinicians. It has only been since R. Gill

brought back 30 pounds of tested crude curare in 1938 that modern medicine had an adequate supply for research work. As mentioned before the task of refining and standardizing of the crude product was undertaken by E. R. Squibb and Sons.

(b) Standardization:

In the standardization of curare, an infusion of alcoholic extract of the drug is prepared. Originally, the lethal dose for mice was determined and 1:10 of the lethal dose started on humans. Now "Intocostrin" is biologically standardized by the "Head Drop" method in the rabbit.

Technique: The curare solution is injected slowly into the ear vein with the rabbit lying face down on a board. The amount is injected which, in two and one-half to three minutes will cause sufficient flaccidity in the neck muscles to prevent the animal from holding its head up. This is the so-called physiological end-point. It is clear cut and similar to that in human beings. From that amount per kilo in rabbits required to reach this end-point, the amount per kilo to produce a similar effect in human beings is calculated. Then the dose is calculated according to weight of the patient. This standardized solution is very stable, retaining its strength indefinitely and not being destroyed by autoclaving. However, room temperature may cause formation of a precipitate. Therefore refrigeration is recommended.

(c) Preparations:

"Intocostrin" (Squibb) is a purified standardized preparation of curare—with most toxic substances removed. It is put up in 5 cc rubber-stoppered vials as a clear transparent amber liquid with each cc equal to 20 mgm potency. Activity is due almost entirely to the crystalloid d-tubo curarine.

(d) Actions:

Claude Bernard made the original writings with regard to the physiology of curare. He showed:

(i) The site of action is the myoneural junction.

(ii) The drug must be administered parenterally to be effective.

(iii) The sensory mechanism is not affected.

(iv) The action is reversible.

(v) The cardiovascular system is not affected directly.

Couty and de Lacerda showed that with some types of Strychnos curare;

(i) Vasomotor paralysis—fall in blood pressure.

(ii) A convulsive action. This was also demonstrated by Tillie in 1890 and by Cash in 1901.

Other workers have shown that the essential action is interruption of nervous impulses at the neuro-muscular junction probably by neutral-

izing or inhibiting that action of acetyl choline (which is the fundamental neuro-muscular stimulating mechanism.) The action of curare is selective. It acts upon all straited muscles in the following order:

(i) Muscles innervated by the cranial nerves.
(ii) Muscles of the trunk and extremities.
(iii) Muscles of respiration (affecting the diaphragm last).

Note that the sequence with which these muscles are affected depends on the availability of utilizable oxygen, thus a greater supply of oxygen accounts for a decreased susceptibility to curare depression. The following physiologic effects are seen two and one-half minutes after intravenous injection and ten minutes after intramuscular injection:

(a) Heavy eyelids.
(b) Bilateral ptosis.
(c) Nystagmus.
(d) Strabismus.
(e) Diplopia.
(f) Weakness of head and neck muscles.
(g) Inability to raise head and neck.
(h) Loss of facial expression (a "nasal smile".)
(i) Slow hesitant speech with weakness of jaw muscles.
(j) Weakness and paralysis of spinal muscles.
(k) Complete paralysis of the extremities.

According to Bennett these paralysing symptoms follow the same order as the progressive symptoms of a patient with myasthenia gravis. Therefore, curare is contraindicated in patients suffering from this disease. It is to be noticed that before its final peripheral action develops, there is depression of the respiratory centre (Felger).

Curare also has a very mild effect on smooth muscle by interruption in the transmission of impulses across sympathetic ganglia (i.e., curare is capable of acting anywhere in the nervous or muscular systems where acetyl choline is the chemical mediator). Thus although the smooth muscle is not directly affected after curare administration, the intestine quiets down and becomes much less distended. In like manner as shown by the electrocardiogram, the cardiovascular system is not affected directly. However some hypotension does result due to:

(a) Interference in synapse of the sympathetic ganglia.
(b) Widespread and complete muscular relaxation causing atonia which does not aid venous return. Cullen disagrees with the work of some investigators and claims that the action of curare on the gut is due to direct action on the effector muscle cells.

It must be realized that curare is not an analgesic or an anaesthetic agent. Thus, after "Intocostrin" administration, the unanaesthetized patient remains well oriented, free from mental confusion even to the point of respiratory arrest. However, two other curarizing solutions:

(a) Erythroidine

(b) Quinine methyl chloride

do cause confusion, disorientation and circulatory changes.

After subcutaneous or oral administration, curare has no effect. With intravenous injection, the maximum effect is obtained in one to two and one-half minutes. With intramuscular injection, maximum effect is obtained in seven to fifteen minutes.

Elimination is very rapid, being apparently complete in ten to fifteen minutes, due to destruction in the liver and excretion by the kidneys. The most important factor in lethality is the rate of absorption. In lethal doses, death by asphyxia occurs due to respiratory paralysis. It has been estimated the amount of drug necessary to produce curarization in the human being is 65% of the fatal dose. There is little cumulative action, thus curare can be given in repeated doses often. However, recent animal experimentation has shown that a second dose is more effective than the first. This would indicate that there is considerable prolongation of effect of the active curare even though the clinical signs of curarization may have disappeared.

Perlstein and Weinglass have shown the fatal effects of prolonged curarization in experimental animals, despite the maintenance of artificial respiration. This lethal effect is hastened by atropine. Although the mechanism and exact cause of death are not precisely known, the heart seems to be principally affected. (Irregular slow pulse, dilated heart, congested liver at necropsy). We may deduct that this effect precludes the clinical use of curare for prolonged periods, e.g., tetanus. We might also suggest that a detailed study of the action of curare on the known enzymatic systems of the various organs is indicated.

An overdose of curare results in diaphragmatic paralysis. The Indians knew of antidotes for curare poisoning and how to use them. However, these were thoroughly mixed with superstition and voodoo, bleeding by free incision of a wound resulting from a curare-laden weapon, ligation above the site, liberal applications of rock salt locally plus copious amounts of concentrated salt solution orally. Raleigh died before he discovered their cure. Modern treatment for overdose consists of:

(a) Adequate artificial respiration and oxygen inhalation.

(b) Prostigmine—the specific anti-curare drug.

(c) Induction of artificial convulsions; Sollman recommends stimulation of the sciatic nerve.

3. *Clinical Applications*

Historically curare has been used for a variety of conditions—among which are:

1. Rabies
2. Tetanus
3. Epilepsy
4. Chorea
5. Muscular rigidities.

Today the therapeutic use of curare resolves itself around the following:

1. An adjuvant to anesthesia
2. An adjuvant to electroshock therapy
3. Those fields where muscular activity and spasticity dominate the picture, as in;
   (a) Spastic paralysis
   (b) Cerebral palsies
   (c) Spasmodic torticollis
   (d) Huntington's chorea
   (e) Little's disease
   (f) Some types of Parkinsonism
   (g) Multiple sclerosis
   (h) Dystonia musculorum deformans.
4. The treatment of Tetanus.
5. The diagnosis of Myasthenia gravis.
6. Orthopedics—e.g., to secure muscular relaxation and early reduction of a fractured femor.
7. Bronchoscopy and langugspasm.

We shall consider each of the above mentioned conditions in some detail:

1. *An Adjuvant to Anesthesia*

During the last five years curare has come into widespread use in the field of general surgery. The technic of administration is as follows: After premedication with morphine and scopolamine the patient is anesthetized with cyclopropane or pentothal sodium induction followed by cyclo, and is held at the level of the second or third plane of stage three. Immediately after the skin incision curare is administered by the intravenous route (over a period not exceeding 10 seconds) and repeated, if necessary, at three to five minute intervals till the optimum effect is obtained. This is evidenced by:

(a) Complete muscular relaxation.

(b) Quieting of intestinal peristalsis.

The initial dose averages .06 gms., with a second dose of .04 gms., and subsequent doses of .02 gms. This makes for an average total dose of .0925 gms. (Cullen) or .070 gms. (Smith).

Excellent abdominal relaxation results in approximately 2½ minutes, which is always accompanied by some respiratory depression. In some this progresses to complete loss of intercostal function but never to complete respiratory arrest. No undesirable circulatory effects are seen and adequate respiratory exchange reappears about three-quarters of an hour before muscle tonus returns. It is interesting to note that curariform properties are also seen with ether, pentothal sodium, and tribromethanol (avertin). This has been proven experimentally in dogs by demonstrating an inhibited contractile muscular response to injection of acetyl choline or to stimulation by electricity. Such an effect is most marked with ether; because potassium ions have a striking anti-curare action and ether increases the muscle response to potassium. Practically speaking pentothal-curare anesthesia has been used successfully on numerous occasions. However, we must consider the following:

(a) Pentothal has a curariform action.

(b) Both pentothal and curare are respiratory depressants.

(c) A precipitate is formed (presumably pentothal) if the same needle be used for both injections. But note there is some evidence to show that this precipitate is soluble in plasma.

The use of curare promises to be one of the greatest aids in the field of anesthesiology. In abdominal operations with patients that resist anesthesia (as in heavy muscular individuals who are also heavy drinkers and smokers) or when a "spinal belly" is desired a cyclopropane-curare combination is the modern method of choice. But we must realize that curare is not a universal substitue for spinal block. Such a cyclo-curare technique results in the following:

(a) Excellent muscular relaxation—which facilitates exposure, makes the technical work easier, and thus causes less trauma.

(b) Permits maintenance of a relatively light anesthesia. Thus it is not necessary to "push" down into the lower planes in order that adequate relaxation is obtained. Such a "pushing" technique is not without dangerous sequelae.

(c) Although respiratory depression is marked it is of but short duration and only requires artificial respiration or a physiological antidote in approximately 12% of cases. In fact pulmonary ventilation with cyclo-curare is better than when cyclo alone or other agents are pushed far enough to give the same degree of relaxation.

(d) Further, pulse irregularities with cyclo-curare are fewer than with higher concentrations of cyclo alone.

There are few contraindications to the use of curare in anesthesia. They are:

(a) Myasthenia gravis.

(b) The non-availability of adequate and efficient artificial respiration.

(c) The presence of impaired renal function—which may heighten an otherwise harmless effect.

2. *An Adjuvant to Electro-Shock Therapy*

Present day treatment of the affective disorders, particularly the depressions, by the induction of "grand mal" seizures is an established and highly effective procedure. The recent introduction of the electric shock method has been a material improvement over previous methods (such as insulin or metrazol shock). However, trauma is still an all important but neglected factor in convulsive therapy; and the traumatic hazards have not been eliminated by the adaption of electroshock. These traumatic complications are not confined to the vertebrae and long bones; with insufficient attention being paid to the visceral complications in the form of petechial hemorrhages, increased incidence of Tuberculosis, etc.

It is the opinion of Cash and Hoekstin that straight unmodified electroshock treatment is unjustified. Many modifications of convulsive shock treatment have been tried, including:

(a) restraint
(b) hyperextension
(c) preliminary insulin coma
(d) spinal anesthesia
(e) preliminary upbuilding (calcium, viosterol), etc.

But none of these proved to be 100% successful. The introduction of preliminary curarization increases the scope of usefulness of convulsive shock therapy and makes the treatment available in cases where it might otherwise be contraindicated.

By the use of preliminary curarization, muscular contractions are markedly softened with the elimination of all serious traumatic complications. In clinical doses, its action proved to be restricted to the myoneural junction as a direct antagonist to acetyl choline producing a partial block of motor impulses. Dose: Curare 1 mg./2 pds. body weight intravenously taking 60 seconds. If given too fast a shock-like action may be produced with a fall in blood pressure and shallow respirations. If given too slowly, curarization may be incomplete or

absent. Again briefly, the symptoms following the injection are: Hasiness of vision, ptosis, nystagmus, relaxation of jaw, and facial muscles, sensation of tightness in throat, dysphagia, huskiness in voice and weakness of muscles of trunk and extremities. At this point, the convulsion is introduced with the result that the muscular contractions are markedly modified. It is necessary to exercise reasonable amount of caution with the use of curare. After the treatment, the angles of the jaws should be supported and if there is a great deal of stridor, an airway should be used. By the time the patient has regained consciousness, the effect of curare has worn off. Prostigmine for intravenous injection should always be immediately available.

Contraindications to this treatment are the same as outlined previously plus:

(1) Active pulmonary infection.
(2) Acute febrile diseases.
(3) Severe thyrotoxicosis.
(4) Thrombophlebitis.
(5) Decompensated heart disease.

We thus see that curare has opened up a new field in shock therapy by enabling the conservative physician to extend its use to patients in the older age groups and to many of those who, because of various physical disabilities, were heretofore denied this beneficial treatment. It is difficult to see how any drug could be more suitable for this purpose than curare because of the ease of administration and the fact that the period of action of curare and electroshock coincide almost idealy. In short, curare meets the existent need better than any other procedure yet produced.

3. *Diagnosis of Myasthenia Gravis*

In this condition it appears that there is some failure in the action of acetyl choline. Physostigmine restores neuromuscular performance in most myasthenic patients. But curare neutralizes the action of acetyl choline and produces artificial myasthenia gravis. The myasthenic patient exhibits marked sensitivity to curare with 1:10 the usual dose and if such a dose is administered curare produces profound exacerbation of the existing symptoms, reaching a peak in 2½ minutes.

These phenomena suggest a specific diagnostic test for the disease. Injection of 1:10 the usual physiologic dose of Intocostrin is a safe procedure if followed by administration of 1.5 mg. Physostigmine methyl sulfate and gr. 1:100 atropine sulphate.

4. *Treatment of Tetanus*

Curare has been used as early as 1894 by Hoche in the treatment of tetanus but he and others of the early clinical experimenters had no

standardized curare preparations. In consequence their results were very variable. Cullen (1942) was the first of the modern group to use Intocostrin for treatment of tetanus. In using curare, the patient with tetanus receives the usual treatment including: debridement of the wound, if necessary, and administration of tetanus antitoxin. Then curare is administered to control the seizures, either intravenously during a spasm or intramusculary to prevent further repetition of convulsions. During the spasm, the intravenous injection relieves the severe contractions and produces freedom from pain in a few seconds. The jaw relaxes, the opisthotonus disappears and the respirations become easier. The frequency of the injections during the illness is determined by the tone of the rectus abdominis muscle, but usually 50 mg. of curare will keep the patient comfortable for approximately three hours and he can move about in bed, cough, expectorate, drink, defecate, etc., which improves his condition greatly and facilitates nursing care tremendously. In contradistinction to spinal or basalances no ill effects have been seen following its administration although the necessary equipment for artificial respiration and prostogmine should be constantly at hand. The true value of curare as a therapeutic agent for tetanus has not been determined as yet and further investigation is required.

5. *Spastic Neurological Disorders Characterized By Muscular Hyperinnervation*

Intocostrin is given intramuscularly every four hours, the dose being individualized by the trial and error method. Curare is not curative but does produce muscular relaxation which gives the physiotherapists an opportunity for muscular re-education and training. Further, it noticably reduces hypertonia, tremer, and involuntary movements producing significant relief without painful spasms.

CONCLUSION

In conclusion, we see that Gill's description of curare as the "Genie in the Ampoule" is most apt. It is indeed, as are most potent drugs, a double-edged sword that can kill as well as cure. So far we have the story of the transformation of a crude drug from the kettles and gourds of the Indian witch doctors to the biological standardization and sterile ampoules of modern medical science. Other chapters in this story remain for time to tell. However we are sure that you will agree that enough has already been revealed to gain for curare a place of definite use in our pharmacopoeia, and a most essential position in the anaesthetists armamentarium.

A History of the Plague*

By PETER A. RECHNITZER, '48

. . . . strangely-visited people,
All swoln and ulcerous, pitiful to the eye,
The mere despair of surgery, he cures,
Hanging a golden stamp about their necks,
—William Shakespeare.

FEW diseases have scourged the world more severely and produced more profound effects upon it, than has the plague. Since its first recorded visitation in 430 B.C. until the present day, this pestilence has killed millions of people, has shaken the foundations of civilizations, and has profoundly influenced social customs and religious modes of thought. It has indiscriminately killed king and cobbler, rich and poor, age and youth, bringing with it throughout its existence immeasurable sorrow.

Thucydides' description of the great plague of Athens in 430 B.C. is a model of its kind and reads like the case report of a master physician: "The body internally was not so very hot to the touch, nor yet pale. It was of a livid color inclining to red and breaking out in pustules or ulcers."

The first great epidemic was in the sixth century after Christ in the reign of the Roman Emperor Justinian. Beginning in Egypt, it spread to Constantinople, thence to Gaul and England, leaving in its wake weakened nations.

In the fourteenth century a devastating epidemic swept through Europe. It has colorfully and gruesomely been called "The Black Death" and has been commonly described as the greatest physical calamity which nature has inflicted upon the human race.

The disease then ravaged for three hundred years, appearing in sporadic epidemics throughout Europe and Asia, and bringing with it a train of misery and famine.

In 1664 an epidemic flared up in England, developing into the "Great Plague of London," which killed one out of every four persons. It has been made familiar to us by diarists of the time, contemporary historians, and novelists of later days.

With the exception of the outbreak in Marseilles in 1720, the eighteenth century saw a decline of the disease, but during the nineteenth century the plague flared up in virulent outbreaks throughout the East where the ignorance and religion of the peoples made preventive measures difficult.

With the twentieth century the disease has subsided, but has not become extinct. Sporadic outbreaks have occurred in the United States and it is still a major problem in India and China.

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The supposed causes of the plague have reflected clearly the knowledge, or rather, the ignorance of the people of the period concerning disease. Not until 1894, when Kitasato and Yersin independently discovered the plague bacillus, was the true etiology recognized.

The principal cause of the Black Death of the fourteenth century was thought to be the result of a grand conjunction of the three superior planets Saturn, Jupiter, and Mars, which took place, according to Guy de Chauliac, on the 24th of March, 1345. The people believed that conjunctions of planets prognosticated great events; revolutions of kingdoms, new prophets, destructive plagues, and other occurrences which bring destruction and horror to mankind. However, that contagion was recognized by Guy de Chauliac, a prominent physician of the day, is evinced by his advice to Pope Clement VI to shut himself up while the pestilence raged.

The medical faculty of Paris, the most celebrated of the fourteenth century, when asked to present its opinion as to the causes of the Black Death, delivered these strange precepts: that the constellations, which combated the rays of the sun, exerted their powers and struggled violently with the sea, forming foul vapours, which alternately rose and fell for twenty-eight days. At last the sun acted so strongly on the sea that it attracted a great portion of the latter and the waters arose in the form of a vapour. The sun was unable to consume this corrupted moisture, so it spread itself throughout the air and enveloped places on the earth. These French physicians predicted that within ten days the mist would be converted into a deleterious rain, whereby the air would be much purified, and they further advised the people that as soon as the rain fell they were to protect themselves from the air, the ascribed cause of the Great Mortality. This unconvincing edict certainly reflected no credit on either the medical faculty of Paris or the fourteenth century in general.

It was the unhappy lot of the Jews to fall prey to the suspicion of the people, concerning the Black Death. They were accused of poisoning the wells and consequently were regarded as the anathema of Europe. They alone were convicted of having brought this fearful mortality upon the Christians. The Jews were helpless—their every act magnified suspicion into certainty in the eyes of the people and they were persecuted with relentless cruelty.

In the seventeenth century the cause of plague was still an enigma. The more learned writers believed the infection was due to four causes, of which the first and most important was supernatural. The plague was God's instrument for the punishment of sin and the people realized the need for preserving spiritual as well as bodily health in order to ward off the disease. The second cause was corruption of the air. Shakespeare includes both in *Timon of Athens* (iv) (iii)

"— a planetary plague, when Jove
Will o'er some high-vic'd city, hang his poison
In the sick air."

Thirdly, the opinion that the conjunction of the stars and the aspect of the planets controlled the nation's health was still widespread. Ulysses expresses the sentiments of that period in England in the words (Troilus and Cressida) (i) (iii)

"— when the Planets
In evil mixture to disorder wander,
What Plagues, and what portents, what mutiny . . . .
Divert, and crack, rend and deracinate
The unity, and married calm of States
Quite from their fixture."

Astrologers noted that the plague of 1603 in London was preceded by a conjunction of Jupiter and Saturn and just before that an eclipse of the sun. Furthermore, a conjunction of the chief planets in 1625 was followed by an outbreak. These celestial signs, however, were conspicuous only because of the events which attended them. Had the plagues of 1605 and 1625 respectively not occurred, then these hints would have been forgotten, as thousands upon thousands of auguries and suppositions which were current at the period were buried in oblivion.

A fourth cause was aptness of body, and prophylactic treatment varied according to the prevailing humor. Thus the sanguine were bled, the choleric were purged with an infusion of rhubarb, and prescribed treatments were given the phlegmatic and melancholy.

The true cause of the plague remained unknown until 1894 when an epidemic broke out in Hong Kong. The Japanese Government sent Kitasato, a pupil of Koch, and the French Government sent Yersin, to determine the cause of the pestilence. Both of these men were eminently qualified for the work of their mission, and independently each soon succeeded in isolating the specific bacillus. It was found in the faeces, in the contents of the swollen glands, and in the blood. It was found to consist of rods with rounded ends, which take stains more markedly at the extremities than in the middle. Sometimes the germ seems to be surrounded by a capsule. In beef tea it grew in chains and formed a viscid deposit on the walls and bottom of the tube. It also grew on blood agar and displayed but little motility. Thus one of mankind's most odious enemies had been brought to light.

The effects of the plague on mankind can scarcely be envisaged. The whole social, religious, and economic structure of society was disrupted. The plague was one of the forces which weakened the Roman Empire. It changed the course of history in the fourteenth century, and it still contributes to the demoralization of India and China. The history

of the plague may well be regarded as an epitome of the progress of our civilization.

Some conception of the devastating effect of the pestilence on the people may be gathered from Boccaccio's description of the Florentine epidemic of the fourteenth century:

> "When the evil had become universal, the hearts of all the inhabitants were closed to feelings of humanity. They fled from the sick and all that belonged to them, hoping by these means to save themselves. Others shut themselves up in their houses, with their wives, their children and households, living on the most costly food, but carefully avoiding all excess.
>
> "Amid this general lamentation and woe, the influence and authority of every law, human and divine, vanished. Most of those who were in office had been carried off by the plague or lay sick, or had lost so many members of their families that they were unable to attend to their duties, so that henceforth every one acted as he thought proper. . . . Thus it was that one citizen fled from another, a neighbour from his neighbours, a relation from his relations, and in the end, so completely had terror extinguished every kindlier feeling, that the brother forsook the brother, the sister the sister, the wife her husband, and at last even the parent his own offspring, and abandoned them, unvisited and unsoothed, to their fate."

It was believed that the wrath of God being moved to punish the people for their iniquity, would not do so wherever they might be, but would be confined to those who remained within the walls of the city. Therefore, those who were able, escaped from Florence and fled to the country homes of their friends. Thus the poor who had no place in which to seek refuge suffered even more miserably than the rich.

The epidemics of the next four centuries disrupted the social life of the people as profoundly as did the Black Death of the fourteenth century. Families were separated, communal gatherings were prohibited, and the social intercourse of afflicted cities maintained a low ebb. A graphic description of the pathos of the situation in London in 1665 has been written by Defoe.

> "London might well be said to be all in tears; the mourners did not go about the streets, indeed, for nobody put on black or made a formal dress of mourning for their nearest friends; but the voice of mourning was truly heard in the streets. The shrieks of women and children at the windows and doors of their houses,

> where their dearest relations were perhaps dying, or just dead, were so frequent to be heard as we passed in the streets, that it was enough to pierce the stoutest heart in the world to hear them. Tears and lamentations were seen almost in every house, especially in the first part of the visitation; for towards the latter end men's hearts were hardened, and death was so always before their eyes, that they did not so much concern themselves for the loss of their friends, expecting that themselves should be summoned the next hour."

Nor were the religious consequences of the plague less far reaching. Public worship was, to a large extent, laid aside. For apart from the reluctance of the citizens to congregate in large numbers, most of the clergy had abandoned their parishes and fled to the country. Many ignorant laymen, who had lost their wives and dared not remain in the ravaged cities, crowded into the monastic orders to share in the respectability of the priesthood and in the rich heritages which fell to the church from all quarters.

The populace grew to regard death from the pestilence with an air of resignation. All minds were directed to the contemplation of futurity; and young children, whose actions are not usually followed by repentance, were frequently seen, while suffering from the plague, engaged in fervent prayer and songs of thanksgiving. An awesome sense of contrition seized Christians everywhere; they resolved to forsake their vices and make restitution for past offenses before being summoned to face their Maker. A historian of the fourteenth century has written—"The lamentation was piteous; and the only remaining solace was the prevalent anxiety, inspired by the danger, to prepare for a glorious departure; no other hope remained—death appeared inevitable. Many were hence induced to search into their own hearts, to turn to God, and to abandon their wicked courses."

During times of major catastrophes and extreme destitution, the rise of heretical religious, and political doctrines is rife. Thus, plague ridden, poverty stricken fourteenth century Europe was fertile ground for the growth of fanaticism, and fell easy prey to the religious orders which arose. The story of one such order is one of the strangest in history. The brotherhood of the Flagellants, called also the Brethren of the Cross, or Cross-bearers, took upon themselves the repentance of the people, for the sins they had committed, and offered prayers and supplications to avert the plague. The Order sprang up in Hungary and at first consisted chiefly of persons from the lower class, who were either motivated by sincere contrition, or who used this as a pretext for idleness.

As the brotherhoods gained in repute and were welcomed by

the people with enthusiasm and veneration, many nobles and ecclesiastics joined them, marching through the streets in well-organized processions, with leaders and singers. These Flagellants, their heads covered to their eyes, were robed in somber garments, with red crosses on the breast, back, and cap, and they carried triple scourges tied in three or four knots, in which points of iron were fixed. Wherever they appeared they were welcomed by the people, who listened to their hymns and witnessed their penance. When they arrived at the place of flagellation, they stripped the upper part of their bodies and took off their shoes, keeping on only a linen dress, reaching from the waist to the ankles. They then lay down in a large circle and were ordered by the leader to arise one by one and scourge themselves, amid the singing of psalms and entreaties for the averting of the plague.

The Order rapidly grew in strength throughout Europe and had so powerful an effect that the Church was in constant danger; for the Flagellants gained more credit than the priests. Finally, the monarchial and religious leaders of the various countries prohibited the existence of the Order, and the minds of the fickle people were turned against the Brethren. The latter were now persecuted and thought to be the very cause of the plague.

The part played by the clergy in the epidemics of the fourteenth to seventeenth centuries was, on the whole, not commendable. A few stayed at their posts, helping the sick and comforting the bereaved. The great majority, however, fled from the infected cities to seek refuge in the country. As a result, the morale of the people declined and education was impeded.

Inevitably, such a cataclysm as the plague had serious repercussions on the economic structure of the afflicted countries. During the great epidemics, trade almost ceased; people existed in a state of lethargy, failing to gather their crops and allowing livestock to wander aimlessly without herdsmen in the fields.

The Black Death was accompanied by a fatal murrain among the cattle. Of what nature this may have been can no more be determined than whether it originated from communication with the plague patients or from other causes. As a result of the disease among the cattle and the failure of the farmers to gather their crops everywhere, a great rise in the price of food increased the pre-existing poverty.

In London the plague of 1603 precipitated a growing depression. The increased taxation resulting from the wars with Spain had reacted on trade, and a succession of bad harvests from 1594 to 1598, and again in 1600, caused widespread poverty. The superimposition of the plague on these conditions brought commerce to a standstill. Foreign countries were extremely reluctant to receive goods from England and particularly

from London. There was a general agreement in France not to receive broadcloth from England. Kerseys were made all over the kingdom, in hamlets and villages as well as in large towns, and the French attitude was resented by English merchants endeavouring to seek discrimination between goods from infected and uninfected districts.

In London the flight of the wealthiest citizens had put a stop to much of the local trade. The difficulty of collecting money also hindered business transactions, for no one would pay his debts when the chances were that his creditor would die.

The epidemic of 1603, although great in itself, was completely overshadowed by the London plague of 1665. Yet, even in the former, it is evident the plague was accompanied by grave economic disorders.

Amid the chaos created by the various epidemics, avarice prospered. People, afflicted by an outbreak, existed in utter confusion and succumbed to multifarious imposters, polluting nearly every profession and office of authority.

Hecker, in describing the deterioration of morals during an outbreak, has written: "Covetousness became general; and when tranquillity was restored, the great increase in lawyers was astonishing, to whom the endless disputes regarding inheritances offered a rich harvest."

During all of the epidemics, many of the regular practitioners deserted their posts and great numbers of quacks existed. Admittedly, the method of cure adopted by the medical men prior to the eighteenth century could hardly be called scientific, but at least there was a genuine interest in curing the sick. However, the charlatans argued that luck rather than skill and knowledge was the deciding factor in recovery, and thus sought to justify their nefarious practice upon the ignorance and terror of the people.

It is evident then, wherever a severe plague epidemic existed, there too could be found an economic, social, and moral collapse of civilization. The profound effects which these epidemics had upon the human race may perhaps be ascribed to two main causes—the effect of the enormous mortality upon the imagination of mankind, and the actual diminution in population, which, in many countries, disrupted trade and threw vast tracts of land out of cultivation. . . .

Since the true cause of the plague remained obscure until the late nineteenth century, most of the prophylactic measures adopted prior to that time were necessarily absurd. The preventive methods used were irrational and sprang from an emotional source rather than from a knowledge of basic cause. People who believed the Jews to be the raison d'etre of the plague persecuted them; those who ascribed the pestilence to the will of God spent their days in prayer; while others

attributed the plague to the foul air and kept themselves locked in their houses.

In the fourteenth century the methods of plague prevention, initiated by the laity, consisted mostly in modifying their ways of living. Sometimes two people adopted antithetical formulae. Boccaccio has written:

> "Some there were who conceived that to live moderately and keep one's self from all excess was the best defence; wherefore, making up their company, they lived removed from every other and shut themselves up in those houses where none had been sick and where living was best; and there, using very temperately of the most delicate viands and the finest wines, and eschewing all incontinence, they abode with music and such other diversions as they might have, never suffering themselves to speak with any nor choosing to hear any news from without of death or sick folk. Others, inclining to the contrary opinion, maintained that to carouse and make merry and go about singing and frolicking and satisfying the appetite in everything possible and laugh and scoff at whatsoever befell was a very certain remedy for such an ill."

In most instances, the physicians were as befuddled as the people. Some conceptions of the bizarre prophylaxis fostered by the doctors of the fourteenth century may be gained from the following: poultry and water-fowl, young pork, old beef, and fat meat in general, were not to be eaten. At breakfast the people were advised to drink little, but at supper it was deemed proper to consume clear, light wine. Sleep in the daytime was considered detrimental; it was to be taken during the night until sunrise. Being out in the evening or early morning was dangerous because of the dew. Too much exercise was discouraged.

The prophylactic views published by a few medical practitioners were more reasonable. Santa Sofia advocated the removal of all putrid matter, while Viscount Bernabo was a protagonist of segregation. Unfortunately, these men were in a minority, and superstitious emotionalism governed the conduct of the majority.

By the sixteenth century, attempts at plague prevention were more systematically organized and each community had certain men who were responsible for the health of the inhabitants. For example, in London, England, the man who assumed most of the responsibility during epidemics was the Lord Mayor, the aldermen and the deputy-aldermen. The Lord Mayor was directly responsible to the King and to the Privy Council, the aldermen to the Lord Mayor. The aldermen were required to see that the prescribed plague-orders were properly ex-

ecuted in the wards which they represented. There was a provost-marshal, whose duty it was to serve the Lord Mayor and his men, and who exercised a general supervision over the inferior officials. Subordinate to the provost-marshal were the beadles and constables. The beadles saw that all infected houses were marked. The constables reported to the Lord Mayor the true number of those who died in each precinct, closed and marked infected houses, and arrested idle persons. Thus London made its first real effort to enforce anti-plague regulations.

The instructions of the Lord Mayor were given to the people by the "plague-orders." The first of these appeared in 1518 and was quite primitive. In succeeding years the orders were altered and amplified. They were published at irregular intervals, as demand arose. Twenty plague-orders were delivered to each alderman, one for every deputy-alderman, constable, warden and beadle in his ward, and the rest were posted in public places.

In 1518 the regulations decreed that inspected houses were to be marked with a red cross and an inscription—"Lord have mercy on us" posted for forty days, during which no inhabitants were allowed to leave the premises without carrying a white rod four feet long. In 1574 people living in a household afflicted with plague were allowed to frequent markets, shops, and other open places, only if they carried a white rod at least two feet in length. A paper bearing the words, "Lord have mercy on us" was to be posted on all infected houses and left until twenty days after the plague had ceased in that house. Also, no person who contracted the disease was allowed in the streets until his sore had completely healed.

The sanitary conditions in London at this time were appalling; houses were crowded and filthy; streets were foul with refuse, and no efficient system of keeping them clean had been established. Rivers and ditches received all types of waste matter. Vagabonds and rogues found in the city were the only people who could be employed to clean the streets and rivers. Repeated attempts were made by the authorities to improve sanitation, and at the threat of an approaching plague, their efforts were redoubled. Men, called scavengers, were employed to see that roads were kept in constant repair and free of rubbish. Everyone was commanded to draw ten buckets of water before six in the morning, and pour them in the streets and gutters. Roads were to be swept every morning and evening at six o'clock and the filth was to be collected in piles. People who polluted the rivers and ditches with rubble were threatened with imprisonment.

Cats, dogs, rabbits, and pigeons were thought to be very dangerous in times of infection. The rat was rarely suspected in England, although in the East it had been associated with the plague for a long time. It seems ironical that during epidemics in England the authorities

devoted attention to the slaughter of the rat's enemy, the dog. However, the treatment of dogs changed with the various plague-orders. In 1564 they were killed if found in the streets between ten o'clock at night and four o'clock in the morning. In 1606 all dogs, without exception, were ordered to be destroyed. Defoe has said that during the epidemic of 1665 forty thousand were slaughtered.

The problem of burials always presented itself during epidemics, and the churchyards became so crowded that scarcely any graves could be made without corpses being exposed. Burial regulations prohibited the gathering of crowds at funerals, fixed hours of interment, outlined methods of burial, and made an attempt to limit the fees of profiteering sextons and bearers. The people disregarded these regulations, flocking to churchyards to see the bodies of friends indifferently thrown into the plague-pits. Finally, these abuses were checked by holding all burials at night when the streets were empty. Orders were given to bury all bodies between sunset and sunrise. The bearers used carts to carry the corpses to the graves, and were required to keep to themselves and carry a red wand. This most unpopular office was held by the lowest citizens, who used it to rob the bereaved families. The problems of burials could have been solved either by cremation or by the removal of bodies from the city, but the first was contrary to religious scruples, and the second was impracticable.

During the last two centuries, and especially the last forty years, the plague has been more or less confined to India and China. In these two countries attempts to eradicate the pestilence have met severe religious opposition. Segregation is resisted, and some sects believe it immoral to try to escape disease. In other parts of the world, the plague has smouldered, with occasional outbreaks.

Wars have always predisposed ravaged countries to epidemics. Famine and poverty, those twin monsters of human misery, are now stalking Europe, producing disease wherever they find propitious breeding grounds. . . Let medical science and sociology endeavour to make this a world in which disease and oppression are rarities, and where pandemics and destitution are non-existant.

Science and humanity must work together to combat existing conditions in Europe and Asia, else epidemics of plague, reminiscent of those in the past, might retard the rehabilitation of war torn countries in a post war era.

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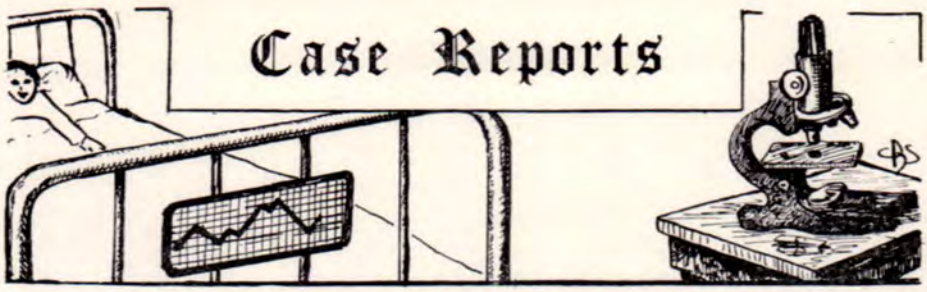


An Interesting Case of Diffuse Goitre With Hyperthyroidism
(Grave's Disease, or Exophthalmic Goitre)

By PAUL KEPKAY, '47

THIS 21-year-old farm lad was admitted to hospital complaining of swelling of his neck.

The history of the present illness extends over a period of three months. Functional inquiry and physical examination reveal the following positive findings:

(a) The Thyroid Gland

Swelling was first noticed by the patient about three months prior to admission. Palpation reveals diffuse enlargements with a maximum neck diameter of 15″. It is soft and elastic in texture with pulsations being both visible and palpable. A definite systolic "bruit" is auscultated.

(b) Cardiovascular System

1. Tachycardia—of 120 per minute. The pulse is full and regular. It is labile (i.e., increased to 150 on moderate exertion).

2. Palpitation—is most noticeable by the patient at night. The cardiac impulse is pronounced and located in an area 1″ in diameter just below and to the right of the left nipple.

3. Blood Pressure—134/52.

4. Vasomotor Instability—is evidenced by profuse sweating (moist skin), ready flushing, and heat intolerance.

5. Abnormal Pulsations—are seen in the neck vessels: the heart beat is clearly transmitted throughout the entire chest (auscultation). No cardiac arrhythmias are demonstrable.

6. Dyspnoea—on severe exertion.

(c) Eye Signs

1. Moderate exophthalmos.
2. Pronounced stare—and infrequent blinking.
3. Lid Lag—when eyeball turned downward.
4. Restriction of convergence.

(d) Motor Phenomena

1. Readily fatigued.
2. Restless and agitated.
3. Purposeless, jerky movements.
4. Fine tremor (fingers).
5. Nervous, "shaky," and *apprehensive;* sleeplessness.

(e) Gastro-Intestinal

1. Appetite—always good; but more pronounced for the preceding two or three months.

2. Weight Loss—gradual loss of approximately 40 pounds during the preceding six months.

(f) Laboratory Findings

1. Haematology—normal except for lymphocytosis of 60%. The W.B.C. is 9,100.
2. Urinanalysis—not remarkable.
3. Blood Sugar & N.P.N.—not remarkable.
4. Bleeding & Clotting Times—within normal limits.
5. B.M.R.—plus 84% (exceptionally high).
6. Blood Cholesterol—128 mgms. % (exceptionally low).

A diagnosis of Diffuse Goitre with Hyperthyroidism was made, this case offering no problem in differential diagnosis. The following *treatment* was instituted:

(a) Bed Rest—with restriction of visitors.
(b) Sedation—with Sodium Amytal.
(c) Psychotherapy—to control irritation, worry, and anxiety.
(d) High Calorie Diet (5,000 calories/day)—in order to meet the increased metabolic requirements.
(e) Propylthiouracil Tablets—150 mgms. per day.
(f) W.B.C.'s—every other day; in order to detect a leukopenia resulting from the toxic action of the propylthiouracil.
(g) B.M.R. Estimation—once a week.

Progress Note:

At the end of *three weeks* the following changes were noted:

1. Weight Gain—of 31 pounds (almost 1½ pounds per day!).
2. Stabilization of the B.M.R.—to between plus 16 and plus 20%.
3. Slowing and Stabilization of the pulse rate—to within normal fluctuations.
4. Marked decrease in nervousness, restlessness, and apprehension. Now able to sleep through the entire night.

5. Subjective symptoms of palpitation and neck pulsations have almost disappeared.

6. Reduction of the propylthiouracil dosage to 100 mgms. daily; because of a W.B.C. of 4,300 on the 12th day. At three weeks the W.B.C. is 7,050.

We may conclude that the patient is being adequately controlled by the propylthiouracil. However, due to the original acuteness of the toxic symptoms it was decided that thyroidectomy was desirable. The patient was started on a pre-operative (10 day course) of Lugol's (iodine) solution; the propylthiouracil was continued (100 mgms. daily).

A subtotal thyroidectomy was performed and the propylthiouracil continued for four days postoperatively. The postoperative course was uneventful except for repeated aspirations due to serious accumulations in the incision. Administration of Lugol's was maintained.

CONCLUSION

A case of diffuse goitre with hyperthyroidism has been presented. It is unique for the following reasons:

1. The marked degree of toxicity as evidenced by the clinical signs and the exceptionally high B.M.R. (plus 84%).

2. The unusually low blood cholesterol level (128 mgm.%).

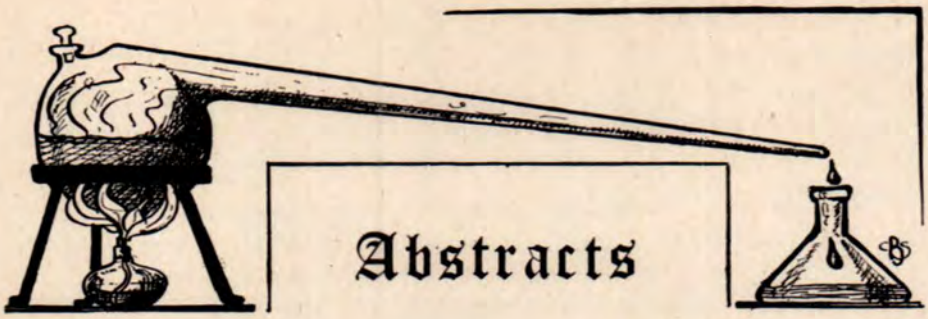
3. The adequate control by the use of propylthiouracil. Minimal toxic manifestations. (Propylthiouracil is not yet generally available to the profession.)

4. The remarkable weight gain.

5. The absence of thyroid "storm" or other postoperative complications—presumably due to adequate pre- and postoperative control with propylthiouracil and iodine. In addition the operation was performed under local infiltration with a minimal amount of general anaesthetic (cyclopropane).

DEADLINE

May 1st, 1947, is the deadline for entering the $34,000 prize art contest on the special subject of "Courage and Devotion Beyond the Call of Duty" (on the part of physicians in war and in peace). This contest is open to all M.D.'s in the Western Hemisphere. The exhibition will take place in conjunction with the A. M. A. Centennial Session at Atlantic City, June 9-13th, 1947. For complete information, write or wire now to Francis H. Redewill, M.D., Secretary, American Physicians Art Association, Flood Building, San Francisco, California, or to the sponsor, Mead Johnson & Company, Evansville 21, Ind., U.S.A.



Abstracts

FURTHER OBSERVATIONS ON IMPERFORATE ANUS

By R. L. RHODES

Annals of Surgery, 123:877, May, 1946

The author discusses techniques used by him for 12 years in the treatment of this condition.

In investigation of the condition he prefers to take X-ray films with the patient on the side with the knees flexed firmly upon the abdomen rather than the plain abdominal film used by other workers.

The main points in treatment are:

1. Several days should be taken to allow the child to develop his lower bowel and anus as much as possible.
2. Repeated X-rays and use of finger pressure in perineum to determine the length of the obstruction.
3. Small incision to permit finger to reach the bowel and not destroy the sphincter.
4. Put incision in region of sphincter and try to cut it only once.
5. When the bowel is reached it is freed and drawn through the incision and secured there. If possible it should be sutured to the skin. Otherwise, it should be anchored to the surrounding muscle. It is opened and the mucosa attached to the skin.
6. Dilation should be done once a week for a year.

Urinary fistulae are not a serious problem because ascending infection will not occur early. If distention becomes great the main cause of anxiety is regurgitation of vomitus. This can be avoided by keeping the baby on the ventral surface.

If colostomy is necessary it should be done high in the sigmoid leaving redundant bowel below so that future surgical reconstruction may be done later.

—H. N. J. BOYD, '47

EPIDEMIOLOGICAL INFORMATION NETWORK

By K. STOWMAN

Epidemiological Information Bulletin 2, October 31, 1946

The author, who is Chief of Epidemiological Information Service UNRRA, discusses the more rapid and reliable epidemiological information now available because of the activity of seven reformed and well integrated offices throughout the world.

These are:

1. International Office of Public Health in Paris giving reports that include the latest sanitary laws.
2. Pan American Sanitary Bureau which covers all of the Americas except Canada.
3. United Nations Epidemiological Intelligence Service which formerly operated under the League of Nations.
4. The Far Eastern Bureau in Singapore.
5. The Pan Arab Health Bureau in Alexandria.
6. Epidemiological Information Service UNRRA, Washington.
7. Epidemic Control Section UNRRA, London.

Besides these, the U.S. Public Health Service and the British Ministry of Health collect international information through their consular and colonial administrations.

The functions of these several agencies are being combined under the Constitution of the World Health organization when this is ratified by the United Nations. In the meantime, the Interim Commission of this organization is unifying their activities.

The author points out that this internation co-operation in sanitary matters has become the field in which world solidarity is the most clearly recognized. His explanation is: "This steady growth is not due to sentimental oratory—which often fails to bring results in other fields—but to practical and far-sighted work on well-defined problems by highly qualified professional men."

—GEO. H. THOMSON, '49

THIOUREA AND RELATED COMPOUNDS IN TREATMENT OF HYPERTHYROIDISM

By A. W. WALKER AND T. S. DONOWSKI

Yale Journal of Biol. and Med.:

This is a review of all that has been written on the use of Thiorea and Thiouracil in hyperthyroidism to date.

18, 527-536, July, 1946.

With thiourea therapy, the iodine content of the thyroid decreases rapidly. This has been shown to be due to the prevention of further synthesis of thyroxin by the drug. Release of preexisting thyroxine is not inhibited. The thiourea content of all body tissues is the same but its specific action is upon thryoxin formation in the thyroid gland. The drug itself is not changed in the body.

Clinically, the accepted dosage of Thiourea is 0.3-1.0 gm. per day and thiouracil 0.6 gm. daily. With this dosage, patients with toxic adenoma and diffuse goitre respond with a drop in B.M.R. to normal in 4-6 weeks. When this occurs, the dosage must be reduced or a hypothyroid state will develop.

Although thiourea is the safer drug and is toxic only in very large dosage, thiouracil is more commonly used today. Toxic reactions occur with this drug in 13% of cases. The most common toxic reaction is leucopenia. Granulocytopenia is less common but is fatal in 1%. When either of these complications arise, the drug should be stopped and penicillin given in large doses.

Dessicated thyroid, by mouth, has proven to be the most satisfactory means of controlling hypothyroidism when it occurs from overdosage of the drugs.

—ARNOLD K. CARTER, '47

THE USE OF ANTHALLAN IN DERMATOLOGY

By L. P. EREAUX AND G. E. CRAIG

C.M.A.J. 55:361, 1946

This paper deals with the use of Anthallan in the treatment of allergic conditions of the skin. It is a relatively non toxic drug and can be used in heavy doses in both infants and adults. The exact mechanism of action is not known but it is believed that it possesses mild anti-histamine activity. It is not a protein and therefore we are not troubled with immune reactions.

One advantage of the drug is that it can be administered orally in capsule or powder form. In some cases, it causes gastro-intestinal irritation and therefore should be administered after food.

The drug is very useful in controlling pruritis and gives relief and comfort to those suffering from allergic dermatoses. Best results are obtained if it is administered as a complementary type of therapy in combination with topical applications, physical agents and sedatives. Side reactions are rare but if they occur are promptly relieved by stopping the drug. Prolonged administration is necessary for best results.

—JOHN R. BARBER, '47

ANASTOMOSIS OF THE AORTA TO THE PULMONARY ARTERY

By WILLIS J. POTTS, SIDNEY SMITH AND STANLEY GIBSON

J.A.M.A. 132:11, Nov. 16, 1946.

Anoxemia due to pulmonary stenosis and atresia has long been recognized as incompatible with normal life. In 1945 a new surgical procedure of anastomosing the subclavian or innominate artery to the right or left pulmonary artery increased the flow of blood to the lungs. However, there is a danger to circulation of the arm involved and a definite hazard to adequate cerebral supply.

Heretofore, direct anastomosis of aorta to adjoining pulmonary artery could not be performed without completely clamping the aorta. This led to paralysis of lower limbs following a temporary anaemia of the spinal cord. However, a new clamp has been designed by two of the authors which occludes most of the aorta, leaving a small channel patent so that the cord will not suffer from anaemia. The operation was performed on three selected patients after it had been performed on 30 dogs, none of which suffered post-operative paralysis.

Technique—After adequate preoperative preparation and proper anaesthesia, the left pulmonary artery is exposed through a posterior 4th interspace incision. This artery is cleared distally and proximally, then occluded for two minutes to determine the effects of temporarily clamping the artery for anastomosis. The aorta is now dissected from its bed, double-tieing the intercostals arising from that segment and cutting the intercostals between the ligatures. The clamp is applied *slowly* to the freed aorta so that blood pressure can accommodate itself to the greatly narrowed channel. Adjacent incisions (approximately 9 mms. in length) are made in aorta and left pulmonary artery so that when the open edges are anastomosed, adventitia to adventitia, these vessels possess a normal anatomical relationship. The aortic clamp is slowly released and removed, the lung is re-expanded and the outer incision closed.

Case Report—Three girls, aged 21 months, 11 years and 8 years, each showed a typical history suggestive of the Tetralogy of Tallot. All three withstood the operation and were given 100,000 units of penicillin post-operatively with 30,000 units every three hours for the next ten days. The two younger girls showed a successful recovery; the oldest girl died 36 hours post-operatively.

Comment—This new operation is not simple and not without danger. However, it promises to be of help to those patients whose condition is otherwise hopeless.

—G. W. BOND, '48

INFECTIOUS HEPATITIS

By H. M. MURPHY

N.Y. State Journal of Medicine, 46:2281-2285, Oct. 15, 1946.

Observations of some 3,000 cases in an Army General Hospital in Italy and France are presented by the author.

Clinically, two-thirds of cases had an acute onset with chills, fever, anorexia, nausea, emesis, upper respiratory symptoms, aching, abdominal distress and fatigue. The urine became dark in one to four days after the onset of symptoms, followed in one to three days by the appearance of icterus. The other one-third of cases showed a more prolonged, afebrile onset with milder prodromal symptoms, the icterus appearing in one to four weeks. It was found that the more rapid and acute the onset of symptoms, the more rapid was the recovery. After appearance of the icterus, the distressing symptoms disappeared in a few days. Fatigue and weakness were often persistent.

Physical findings included lymphadenopathy, especially cervical, enlarged liver in icteric stage with some liver tenderness and moderate splenomegaly in 40% of cases. The icterus usually lasted two to three weeks.

Laboratory findings included usually a normal leucocyte count with a relative lymphocytosis, normal sedimentation rate, elevated icteric index, elevated serum phosphatase (5-10 Bodansky

units), which was of diagnostic aid in pre-icterus period, a positive cephalen flocculation test, increased prothrombin time in severe cases—with nose bleeds, 1-3 plus albumin in the urine and mild to moderately depressed hippuric acid excretion test in late stages of severe cases.

In treatment, bed rest till all symptoms disappeared is the most important feature, with gradual resumption of activity. An adequate nutritious diet high in carbohydrate and protein and low in fat is essential. Plasma can be used freely during early stages where there is nausea and vomiting. Fresh blood transfusions offer the best way to raise depressed prothrombin production, vitamin K having no effect because of the liver damage. No specific drugs were found to be of any value.

—R. TRELEAVEN, '47

EFFECT OF BENZEDRINE ON FATIGUE IN SOLDIERS

By LIEUT.-COL. W. SOMERVILLE

C.M.A.J., 55:470, November, 1946

Two separate experiments were carried out to determin the effect of benzedrine on physical and mental fatigue.

In experiment A the performance time and rifle-firing ability of two groups of soldiers were compared in the fresh state and after a fatiguing exercise. One hour before the end of the exercise one group received 15 mgms. of Benzedrine each; the other group received an inert substance.

In experiment B three groups were used, two groups took divided doses of benzedrine totalling 30 mgms. and 35 mgms. whereas the third group received an inert substance. In none of the cases were the individuals aware of which substance they received.

In tabulating the average performance time and rifle-firing ability in each group in both the fresh and fatigued state it was noted that there was no appreciable improvement due to the administration of benzedrine.

Similar experiments carried out on army officers doing staff problems showed no significant effect on military efficiency after the use of benzedrine.

On the basis of these experiments benzedrine could not be recommended to avert physical and mental fatigue in soldiers.

—RUBY RAIKOV, '49

MOTOR DISORDERS IN NERVOUS DISEASES

By TRACY PUTNAM & ERNEST HERZ

This fine atlas was originally intended as a supplementary to a collection of teaching films on motor disorders in nervous diseases. With its host of illustrations and summaries of the neuroanatomy and physiology of each subject heading, it should fill an empty place in the teaching of neurology.

In neurological investigation, the evaluation of motor functions occupies the main part of all the different examinations and tests. Our diagnostic considerations are to a large extent governed by the normality dysfunction or distortion of motor functions. A chapter is devoted to each of the following: involuntary movements, disorders of gait and co-ordination, muscle status, reflexes, skilled acts and each of the cranial nerves. Each group of phenomena is approached from a physiologic or anatomic structural discussion of the underlying factors. The results of lesions in animal experiments have been given for further explanation.

Many illustrations including in many places, enlargements from the moving picture films, seem to make even more clear the nature of the motor disorders in nervous diseases.

The book is intended to be a preparation for diagnostic considerations at the bedside and should be read by every student undergraduate and postgraduate.

—C. G. DRAKE, M.D.

PHYSICAL SIGNS IN CLINICAL SURGERY

By HAMILTON BAILEY

10TH EDITION

The new tenth edition of this Hamilton Bailey test is one which should serve to maintain this volume in the best seller class of medical

literature. It most certainly should continue to be a valuable guide and reminder to student and graduate alike.

As in previous editions, the author is successful in keeping the context strictly within its intended limits. Concise, clearly written and excellently illustrated, the book contains 573 photographs and diagrams, almost 100 more than its immediate precursor.

The presentation is simple and easily referable. For example, the chapters on hip joint, or gastro-intestinal tract are found under the respective headings, and their signs and elicitation quickly obtainable.

Brevity with sufficiency is the keynote of this book and in the same vein we say, "Buy it; it's money well spent."

—E. R. PLUNKETT, M.D.

NARCOTICS AND DRUG ADDICTION

By ERICH HESSE, M.D.

1ST EDITION

PHILOSOPHICAL LIBRARY INC. (NEW YORK), 1946

This is a book that, besides being quite comprehensive, is well-written and interesting. The author classifies these toxic substances into narcotics and stimulants, dealing with their habituation, addiction, dehabituation and finally, the legal measures enacted against them. This book is originally German and the translation by Frank Gaynor does it full justice.

There is a good index of authors and authorities quoted, of substances and topics and quite an extensive bibliography. Hesse gives a good, detailed description of each toxic substance, dealing briefly with its history, chemical make-up and deleterious effects on the human race. Unlike other texts, he offers some suggestions as to their control and elimination.

It is a book well worth reading and I think that every doctor should read it for his own benefit and to guide him in the use of these drugs.

—A. DIFRANCESCO

THE FACE IN HEALTH AND DISEASE

By MAX THOREK

F. A. DAVIS COMPANY (PHILADELPHIA), 781, 636 ILLUSTRATIONS (1946)

Dr. Thorek's book fills a long-standing need. A subject of such prime importance in every branch of medical practice is surely deserving

of special treatment and at last we have a text which covers the field properly.

It would be difficult to think of any aspect of the subject which Dr. Thorek has not dealt with adequately in his book. There are excellent chapters on the historical background of the study and on the evolution of the human face. Embryology and anatomy are dealt with in considerable detail. Special attention is devoted to the appearance of the face in various emotional and physical states and its variations in the racial groups. A sideline of special interest is a chapter on facial adornments, decorations and customs.

The normal and pathological appearance of the various elements of the face—eyes, mouth, nose, hair and so on, are all dealt with in turn. There are special chapters devoted to such subjects as dermatological conditions, neurological disorders, endocrinology, mental diseases, diseases of children, and their facial manifestations.

The photographs are exceptionally good and follow the subject matter very well from page to page. Perhaps the only criticism to be offered is that none of the photographs are in natural colour: this would have been very valuable in some instances. Attempts have been made to retouch some plates with colour to demonstrate cyanosis, jaundice, etc., but these are very poor.

This should prove to be an interesting book to student and graduate alike. Merely studying the pictures would be time well spent. The subject matter is written in a straightforward manner and makes fairly easy reading in spite of the intensive treatment of the subject. All in all, a book to be highly recommended.

—CAM WALLACE, '48

QUANTITATIVE CLINICAL CHEMISTRY. INTERPRETATIONS

Volume I

By PETERS AND VAN SLYKE
2ND EDITION

WILLIAMS AND WILKINS CO. (BALTIMORE), pp. 1041 (1946)

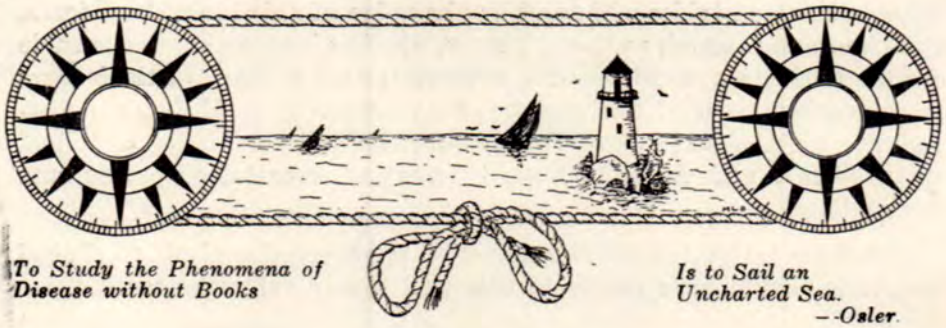
The first volume of this long-awaited second edition of Peters and Van Slyke constitutes the most ambitious comprehensive reference work in pathological chemistry and is pre-eminent in the field. This work treats the normal and pathological physiology of energy metabolism, carbohydrates, lipids, and proteins with special emphasis on the latter section.

The well arranged index, extensive bibliography and the many

illustrations and tables add much to the value of this book to students, clinicians and research workers. Peters, who has been mainly responsible for the production of this volume, enjoyed the aid of many of the leaders in the various fields of biochemistry, for example, C. N. H. Long (carbohydrate metabolism), J. S. Fruton and A. White (protein and lipid metabolism), and A. E. Wilhelmi (creatine, creatinine, purine and pyrimidines).

Anyone interested in the application of chemical analysis to clinical diagnosis should have access to this well known reference work.

—J. M. R. BEVERIDGE, PH.D.
—D. L. OESTREICHER, M.D.
—R. H. PEARCE, B.SC.



To Study the Phenomena of Disease without Books

Is to Sail an Uncharted Sea.
—Osler

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Annals of eugenics
Blood: the journal of hematology.
British journal of pharmacology and chemotherapy.
Public health economics.
Universities quarterly.
January 14, 1947.

Editorial

THE twenty-fifth anniversary of the discovery of insulin was appropriately celebrated at the Medical School of the University of Western Ontario in a three-day conference, November 20, 21, 22. The present issue of the Medical Journal is devoted to addresses given on that occasion by Dr. Elliott P. Joslin, Dr. E. P. Watson and Dr. W. P. Tew. It was in an article by Dr. Moses Barron, who also took part in the anniversary celebrations, that Sir Frederick Banting, then an instructor at "Western," found the clue which led to his famous discovery. The volume of Surgery, Gynecology and Obstetrics in which this paper appeared is proudly preserved in the Medical Library; the crucial paragraph which caught Banting's eye and fired his imagination was later underlined by him at the librarian's request and the first page bears his signature. This memento should serve as a stimulus to those who use the library, a reminder of the rich possibilities which yet lie hidden in print, awaiting the eye of imagination.

The story of Banting's subsequent struggle is one of the great romances of medicine. But medicine can never pause, can catch its breath only for a moment even on such a summit of achievement as this. Since the discovery of insulin the exploration of further ranges of the subject has never ceased. What progress has been achieved and what the present moment has to teach of the management of diabetes is presented by leading authorities in the following pages.

LLOYD STEVENSON.